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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/783,580 | 02/15/2001 | Lawrence E. Cornett | 023533-0113 | 4347 |

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3000 K STREET NW
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EXAMINER

PRIEBE, SCOTT DAVID

| ART UNIT | PAPER NUMBER |
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1632

DATE MAILED: 01/15/2003

16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/783,580

Applicant(s)

Cornett et al.

Examiner

Scott D. Priebe, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Nov 7, 2002
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5, 8-36, 38, and 44-57 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 8-36, 38, and 44-57 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 15 6) ☐ Other:

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DETAILED ACTION

The amendment and response filed 11/7/02 has been entered. Claim 37 has been cancelled. Claims 1, 3-5, 8, 9, 18, 20, 30, 32, 33, 35, 38, 44-50 have been amended. Claims 51-57 have been added.

The amendment to the claims filed on 11/7/02 does not comply with the requirements of 37 CFR 1.121(c) because claims 8, 38, and 49 each contain a bracketed phrase (lines 1-2), which appears from the marked-up copy that it should be deleted. Amendments to the claims filed after March 1, 2001 must comply with 37 CFR 1.121(c).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

Only the English abstract of WO 97/35963 reference was considered, the remainder being in Japanese. Applicant provided no information on the relevance of this disclosure to the claimed invention beyond providing a copy of the search report on which it was cited. It is not clear from the Abstract whether the reference is as relevant as or more relevant than the prior art already of record. Should Applicant wish the entire disclosure be considered, a translation should be provided.

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Claim Rejections - 35 USC § 112

Claims 14, 44-48, and 50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are limited, by virtue of amendments to their base claims, to transfection of airway cells, specifically epithelial and smooth muscle cells. Originally claimed embodiments relating to transfection of blood vessel endothelial and smooth muscle cells have been cancelled from the claims. However, these claims recite that the promoter may be an endothelial cell specific promoter. Applicant has failed to indicate where the specification supports the use of an endothelial cell specific promoter for transfection of airway cells; and the original specification does not appear to support such use in the context of the instantly claimed invention. Consequently, these claims include new matter directed to embodiments which do not appear to have been contemplated by Applicant at the time the invention was made. Deletion of “an endothelial cell specific promoter” from claims 14, 44-48, and 50 would overcome this rejection.

Claims 13, 14, 44-48 and 50 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office action of 6/7/02, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

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relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's arguments filed 11/7/02 have been fully considered but they are not persuasive. Applicant has provided the journal article (Exh. 1) cited in the specification for a single species of epithelial specific promoter (page 20, lines 22-24), and an additional article by the same authors (Exh. 2), and articles describing a second epithelial specific promoter (Exh. 3 and 4). With respect to the second promoter, exhibit 3 discloses that this promoter is active only in lung type II and Clara cells. The instant specification makes no mention of these cell types or that they are suitable targets for the claimed method, and provides no guidance that would have directed one of skill in the art to use this promoter (surfactant Protein B promoter) in the context of the present invention. Exh. 5 was published well after the instant application was filed, and its teachings would not have been known to one of skill in the art at the time the application was filed. Thus, these exhibits do not demonstrate that sufficient promoters were known in the art that mere mention of "epithelial cell specific promoter" would allow one of skill in the art to envision a genus of such promoters.

Similarly, Exhibits 6 and 7 describe a single promoter, alpha-actin promoter, specific to smooth muscle cells. The instant specification does not mention this promoter. No evidence of a genus of promoter specific to airway smooth muscle has been provided. Thus, these exhibits do not demonstrate that sufficient promoters were known in the art that mere mention of "smooth

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muscle cell specific promoter” would allow one of skill in the art to envision a genus of such promoters.

Claims 1-5, 8-36, 38, 44-50 remain rejected and new claims 51-57 are rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office action of 6/7/02, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

New claims 55-57 are limited specifically to treating asthma.

Applicant's arguments filed 11/7/02 have been fully considered but they are not persuasive. Applicant argues that any airway disease that can benefit from β 2AR-mediated processes in airway cells are treatable by the claimed invention. However, the specification fails to disclose any such diseases other than asthma, and no evidence has been provided for any other such disease. Only new claims 55-57 are limited to asthma.

The Cornett declaration under 37 CFR 1.132 filed 11/7/02 is insufficient to overcome the rejection of claims 1-5, 8-36, 38, 44-50 based upon lack of an enabling disclosure as set forth in the last Office action because the evidence presented does not demonstrate that any β 2AR was expressed *in vivo*. Declarant simply infers such expression because GFP was expressed. Even if the β 2AR sequence was expressed, one cannot determine from the results presented whether active β 2AR protein was expressed appropriately, or expressed at a physiologically effective

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level, particularly for treating an airway disease such as asthma. The rats used in the experiments were normal, not suffering from an airway disease. The evidence does not show that sufficient transfection and expression was achieved that would have suggested that a disease such as asthma could be effectively treated. Orkin had taught that assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints. The declaration relies only on inference from a qualitative assessment, rather than quantitative, and provides no showing of physiologically relevant expression and activity of $\beta 2AR$, and no assessment of whether such results could be obtained in a subject suffering an airway disease, such as asthma.

Applicant asserts that successful gene therapy for hemophilia B using AAV vectors has been reported, but provides no evidence to support the assertion. Exhibit 9 was provided, which describes an successful attempt at treating SCID by an *ex vivo* therapy approach. The relevance to these very limited examples of successful gene therapy to the claimed invention are neither explained nor clear. Orkin makes very clear that one cannot extrapolate from one gene therapy method for treating one disease, to using other methods and treatment of other diseases; each disease presents its own challenges which must be overcome. Factor and Demoly describe hurdles specific to treating airway diseases, such as asthma, which the instant specification neither accounts for nor teaches how to overcome. As pointed out by Applicant, Factor mentions *in vivo* adenoviral-mediated transfer of $\beta 2AR$ in *normal* mice. However, Factor was published

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after the instant application was filed, and they do not equate this teaching with therapy. In the succeeding paragraph on page 518, col. 2, they teach that significant hurdles existed for asthma gene therapy (after the instant invention was made), and conclude only that there is a realistic promise that some gene therapy may eventually be developed for asthma.

Applicant's final arguments appear to suggest that all that is required for enablement of the claimed invention is transfection of a single cell. However, the only utility taught for the claimed invention is therapy. Thus, the specification must teach how to achieve successful therapy. Orkin had taught that merely obtaining some expression *in vivo* was not sufficient. Applicant dismisses Demoly because Demoly does not provide data from the authors research group. It is unclear how the lack of data from the authors research supports Applicant's conclusion. Demoly is a review of research articles, and provides an overview of what little was known in the art about gene therapy for asthma.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 53 and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 53 and 54 recites the limitation "[T]he method of claim ..." in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 31, from which both depend,

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is not directed to a method. It is unclear whether these claims should depend from claim 31 or a claim reciting a method.

Claim Rejections - 35 USC § 102 & 103

Claims 30-34 remain rejected under 35 U.S.C. 102(b) as being clearly anticipated by Bertin et al. (Proc. Natl. Acad. Sci. USA 91: 8827-8831, 1994) for the reasons of record set forth in the Office action of 6/7/02.

Claims 30, 32, and 33 remain rejected under 35 U.S.C. 102(a) as being anticipated by Kawahira et al. (J. Thorac. Cardiovasc. Surg. 118 (3): 446-451, Sep. 1999) for the reasons of record set forth in the Office action of 6/7/02.

Claims 30, 32, and 33 remain rejected under 35 U.S.C. 102(b) as being anticipated by Kawahira et al. (Circulation 98 (19): 262-268, 1998) for the reasons of record set forth in the Office action of 6/7/02.

Claims 30, 32, and 33 remain rejected under 35 U.S.C. 102(a) as being anticipated by Drazner et al. (J. Clin. Invest. 99: 288-296, 1997) for the reasons of record set forth in the Office action of 6/7/02.

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Claims 30, 32, 33, 35, 38 and 49 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hammond et al. (US 6,306,830) as evidenced by Ping et al. (Microcirc. 3 (2): 225-228, 1996) in view of any one of Kawahira et al. (J. Thorac. Cardiovasc. Surg. 118 (3): 446-451, Sep. 1999); Kawahira et al. (Circulation 98 (19): 262-268, 1998); or Maurice et al. (J. Clin. Invest. 104: 21-29, July 1999) for the reasons of record set forth in the Office action of 6/7/02.

Applicant's arguments filed 11/7/02 have been fully considered but they are not persuasive. The base claims have been amended to recite that the composition is "suitable for airway delivery", and Applicant asserts that this limitation overcomes the cited prior art. However, no explanation is provided to explain why the compositions in prior art are not "suitable". Presumably the prior art compositions could be incorporated into an aerosol, for example, which would make them "suitable" for airway administration. This vague limitation does not place any physical constraints on the nature of the composition beyond that which would also be suitable for other routes of administration. It is again suggested that the claims be amended to recite an aerosol, which would be a physical limitation not met by the prior art.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX numbers are (703) 308-4242 or (703) 305-3014 for any type of communication. In addition, FAX numbers for a computer server system using RightFAX are also available for communications before final rejection, (703) 872-9306, and for communications after final rejection, (703) 872-9307, which will generate a return receipt. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Scott D. Priebe